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HIGHLIGHTS FROM *JACC* IN 2004

Highlights of the Year in *JACC* 2004

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Last year we initiated a new feature in which the editors selected the articles that they judged to be the best of *JACC* in the prior year. Only time will tell which of the many excellent studies we publish will have the greatest impact, or in fact if that description will belong to a report we did not even accept. Nevertheless, we have tried to identify those entries that received the most enthusiastic critiques and were of the greatest interest to the editors.

INTERVENTIONAL CARDIOLOGY: DRUG-ELUTING STENTS (DES)

Several studies were published in *JACC* that show significant benefits of DES compared to bare metal stents (BMS) and may potentially expand the (off-label) indications in areas that have not yet been studied in randomized controlled trials (RCTs).

Lemos et al. (1) performed primary percutaneous coronary intervention (PCI) with sirolimus-eluting stents (SES) in 186 consecutive patients with acute myocardial infarction (AMI) and compared them to 183 consecutive patients treated with BMS in the preceding six months. No significant differences were noted in the incidence of death or re-infarction. Target vessel revascularization (TVR) at 30 days was similar, but a significant difference in favor of SES was present at 300 days (9.4% vs. 17%, $p = 0.02$), mainly due to fewer repeat PCIs. The rate of stent thrombosis was 0% in the SES group and 1.6% in the BMS group. This non-randomized registry is the first report to compare DES with BMS in AMI treated with PCI and shows a durable benefit and no increased risk of stent thrombosis.

In the same registry, Hoye et al. (2) compared 56 cases of de novo chronic total occlusions (CTO) with SES to 28 patients treated with BMS. At six-month follow-up, the binary restenosis rate in the DES group was 9.1% with a mean in-stent late lumen loss of only 0.13 mm. At one-year follow-up, the cumulative survival-free rate of major adverse cardiac events (MACE) was higher in the SES group versus the BMS group (96.4% vs. 82.8%, $p < 0.05$). This small observational study was first to report that SES reduces MACE in CTO compared to BMS, and needs confirmation.

Schampaert et al. (3) evaluated the role of SES compared to Bx-VELOCITY stents in an RCT of 100 patients with small coronary arteries (mean reference diameter 2.65 mm, mean lesion length 14.5 mm). At eight-month angiographic and clinical follow-up, the use of SES was associated with lower binary restenosis (2.3% vs. 52.3%, $p < 0.001$), less in-lesion late loss (0.12 vs. 1.02 mm, $p < 0.001$), higher in-stent minimal lumen diameter (MLD) (2.46 vs. 1.49 mm, $p < 0.001$), less clinically driven target lesion revascularization (TLR) (4% vs. 18%, $p = 0.05$), and improved freedom from MACE at 270 days (96.0% vs. 81.7%, $p = 0.02$). The dramatic impact on late loss in small vessels is similar to the findings in larger vessels and suggests that DES should be the default stenting strategy in these lesions (4).

In an observational study, Iakovou et al. (5) reported the first study on the role of SES in 32 patients with aorto-ostial lesions compared to a variety of BMS. Angiographic follow-up showed less binary restenosis (11% vs. 51%, $p < 0.0001$), late loss (0.21 vs. 2.06 mm, $p < 0.0001$), TLR (6.3 vs. 28%, $p = 0.001$), and MACE (19% vs. 44%, $p = 0.02$) with SES.

Orlic et al. (6) treated 155 consecutive patients with multivessel coronary artery disease (CAD) with a total of 573 SES (mean 3.1 lesions per patient) and showed a MACE rate of 22.3% with 2.7% deaths and 3.6% myocardial infarction (MI) and a TLR rate of 14.3% (but only 6.7% of all lesions). Stent thrombosis occurred in 1.9% of patients, and total stent length was the best predictor of MACE. This first report on multivessel stent placement suggests that multivessel disease will continue to remain a challenge for effective treatment with DES.

Two studies reported either no effectiveness or worse clinical outcomes with other types of DES. In the Actinomycin Eluting Stent Improves Outcomes by Reducing Neointimal Hyperplasia (ACTION) study, Serruys et al. (7) randomized 360 patients to either BMS or two doses of actinomycin-D. A revised follow-up angiographic protocol showed that in-lesion late lumen loss was higher in both actinomycin-D groups compared to the BMS group as was the six-month and one-year MACE, driven exclusively by TVR. In the Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial (8) using the

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paclitaxel derivative 7-hexanoyltaxol within an acrylate polymer membrane mounted on a novel stent design, incidences of early and late stent thrombosis and MI were significantly higher in the 7-hexanoyltaxol arm, leading to premature cessation of enrollment. The investigators and sponsors are to be commended for publishing these unflattering studies that potentially shed light on the clinically relevant differences in drugs, polymers, coatings, and delivery systems. They also reflect the sobering finding that, although pre-clinical models of restenosis with DES may predict angiographic findings, they often do not accurately predict clinical events in patients, questioning the usefulness of such models and how they are tested (9).

PERCUTANEOUS CORONARY INTERVENTION

Primary PCI in hospitals without on-site surgical backup. Wharton et al. (10) presented the Primary Angioplasty in Myocardial Infarction No cardiac Surgery On Site (PAMI No SOS) study, evaluating treatment of thrombolytic-eligible AMI patients with primary PCI in hospitals having cardiac catheterization laboratories but no surgical backup. They compared this group to a cohort derived from the Air Primary Angioplasty in Myocardial Infarction (AIR PAMI) study who underwent transfer to a primary PCI center without thrombolytics. The combined primary end point of 30-day mortality, re-infarction, and disabling stroke occurred in 5.0% of on-site PCI patients and 8.5% of transfer patients ($p = 0.27$). Unadjusted one-year mortality was similar with on-site PCI compared to transfer after adjustment for differences in baseline variables. Transferred patients had a longer mean time to treatment and diminished Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Although observational and non-randomized, this study has significant public health implications as it suggests that primary PCI in patients with high-risk AMI at hospitals with off-site cardiac surgical backup is as safe and effective, and significantly faster than transfer to a surgical facility for PCI. As pointed out in an editorial (11), primary PCI should be the favored approach for ST-segment elevation AMI and it should no longer be acceptable to give thrombolytics when mechanical intervention is available.

Use of PCI in diabetics. Patients with diabetes continue to have poorer outcomes compared to nondiabetic patients even in the current interventional cardiology era. Corpus et al. (12) evaluated the role of optimal glycemic control (HgA1c <7%) following PCI with BMS in 179 diabetics compared to 60 nondiabetics in a single-center retrospective study. At 12 months, diabetics with optimal glycemic control had a similar rate of TVR compared to nondiabetics. However, diabetics with HgA1c >7% had a significantly higher rate of TVR than those with HgA1c <7% (34% vs. 15%, $p = 0.02$). Optimal glycemic control was also associated with a lower rate of cardiac rehospitalization and recurrent angina. This study provides impetus for additional RCTs to study the effects of optimal glycemic control following PCI (13).

Percutaneous treatment of patent foramen ovale (PFO) in cryptogenic stroke. The RCTs evaluating the safety and effectiveness of percutaneous PFO closure devices for the treatment of cryptogenic stroke have not yet been carried out. In a nonrandomized study, Windecker et al. (14) evaluated the risk of stroke recurrence in 308 patients with cryptogenic stroke and PFO, who were treated either medically (158 patients) or underwent percutaneous PFO closure (150 patients) between 1994 and 2000. At four years of follow-up, PFO closure resulted in a strong trend toward risk reduction of death, stroke, or transient ischemic attack combined (8.5% vs. 24.3%, $p = 0.05$). Approximately 50% of the medically treated patients were on warfarin and the remainder were on aspirin. This study suggests that dramatic benefits in reducing recurrent cryptogenic stroke above and beyond medical therapy may be difficult. Carefully selected inclusion and exclusion criteria and appropriate medical therapy will be crucial in the design of future studies to assess the efficacy of this promising treatment (15).

Cost-effectiveness. The issue of cost-effectiveness is becoming more important as it becomes increasingly harder to show benefits in mortality with newer therapies. Two studies published in *JACC* showed the cost-effectiveness of distal protection devices and bivalirudin. Cohen et al. (16) performed an economic analysis of the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial evaluating the GuardWire balloon occlusion device, which reduces MACE in patients undergoing PCI of stenosed saphenous vein bypass grafts. Use of the GuardWire device increased initial procedural costs by $1,600. However, the mean length of hospital stay was reduced by 0.4 days, owing to a reduction in ischemic complications, decreasing follow-up hospital costs, and leading to an overall net cost of $582 per patient. Overall, the incremental cost-effectiveness ratio for distal protection was $3,718 per year of life saved, less than the accepted yardstick of $40,000.

The Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial showed that patients undergoing non-emergent PCI with bivalirudin plus provisional glycoprotein (GP) IIb/IIIa had equal ischemic outcomes but lower rates of major and minor bleeding compared to patients treated with heparin plus routine GP IIb/IIIa. Bivalirudin and provisional GP IIb/IIIa inhibition resulted in an actual cost savings of $375 to $400 per patient, which was primarily due to the lower costs of bivalirudin compared to other GP IIb/IIIa (16).

HEART FAILURE (HF)/CARDIAC TRANSPLANTATION

Use of phosphodiesterase-5 (PDE5) inhibition in HF patients. Recent evidence suggests that use of a PDE5 inhibitor may benefit patients with pulmonary hypertension. Guazzi et al. (17) assessed the acute effects of 50 mg of

sildenafil or placebo on cardiac function, pulmonary hemodynamics, and exercise performance in 16 HF patients and 8 normal subjects. Although sildenafil did not affect ejection fraction (EF) or pulmonary artery wedge pressure in the HF patients, it significantly lowered pulmonary artery pressure (~20%) and increased carbon monoxide diffusion capacity (DL_{CO}). Sildenafil also increased brachial artery reactivity, and during exercise it improved peak oxygen consumption (V_{O_2}), aerobic efficiency (V_{O_2}/W), and ventilatory efficiency (V_E/V_{CO_2}). Although these findings suggest that PDE5 inhibition may be useful for the treatment of chronic HF, further long-term studies are needed to help define this possibility.

Association between loop diuretics and cardiac fibrosis. Recognition of the fact that collagen turnover in the heart is a dynamic and highly regulated process has stimulated interest in defining factors that promote fibrosis as well as new therapeutic approaches to treat this problem. Lopez et al. (18) hypothesized significant differences may exist between loop diuretics in collagen turnover and cardiac fibrosis. The investigators randomized patients with symptomatic HF to either torsemide 10 to 20 mg/day (n = 19) or furosemide 20 to 40 mg/day (n = 17) on top of existing therapy. They found that torsemide but not furosemide significantly reduced cardiac fibrosis in biopsy specimens and indices of collagen synthesis (without change in collagen degradation). These results raise the interesting possibility that loop diuretics might have heterogeneous effects on cardiac fibrosis in HF patients.

A possible explanation for the antifibrotic effects of torsemide was presented by Tsutamoto et al. (19) who determined transcardiac extraction of aldosterone in HF patients treated with loop diuretics. In this study, 60 patients were randomly assigned to receive either furosemide (n = 30) or torsemide (n = 30) for one month. Over this period there were no differences in measures of cardiac function, clinical status, or plasma aldosterone levels. However, the investigators found that there was aldosterone uptake in the heart in the patients randomized to furosemide but not in the group that received torsemide. Because aldosterone is believed to play a critical role in promoting remodeling of the heart and, in particular, increased deposition of fibrous tissue, results of this study support the findings of Lopez et al. (18) noted in the preceding text, which demonstrate antifibrotic effects of torsemide.

Value of in-hospital initiation of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers. Despite abundant evidence that ACEIs and beta-blockers produce substantial improvements in the clinical course of HF, surveys consistently indicate that these therapies are underutilized. Two *JACC* articles in the past year indicate that this important deficiency can be improved. Butler et al. (20) evaluated long-term outpatient ACEI use following an index HF hospitalization. They found that 67% of patients were discharged on ACEIs but that nearly one-third of them failed to refill their prescription by six months. In contrast, of patients with no discharge order for ACEIs, only 12.7% had filled such a prescription by 30 days. Interestingly, neither demographic characteristics, EF, or the presence of hypertension or diabetes was related to the filling of an ACEI prescription. The investigators concluded that for HF patients who are discharged on ACEIs, there is a significant decline in use after discharge. Patients not discharged on ACEIs are unlikely to be started as outpatients.

A possible solution to the issues raised by Butler et al. (20) comes from Gattis et al. (21) who report the results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) study. This study prospectively evaluated whether pre-discharge carvedilol initiation in stabilized patients hospitalized for HF increased the number of patients treated with beta-blockade at 60 days without increasing side effects or length of hospital stay. For the primary end point of the study, 91.2% patients randomized to pre-discharge carvedilol initiation were treated with a beta-blocker at 60 days post-discharge as compared to 73.4% of patients randomized to initiation post-discharge. Moreover, pre-discharge initiation was not associated with increased serious adverse events or increased hospital stay. The researchers concluded that the excellent uptake of beta-blocker therapy seen in this study can be attributed to extensive pre-discharge treatment planning, and that this is further improved by in-hospital initiation of therapy.

An issue of practical importance is the order in which the neurohormonal blocking agent drugs should be started. Traditionally, an ACEI is started first based in part on the order in which the agents were approved for the treatment of HF. Sliwa et al. (22) investigated whether this practice is really optimal. In a single-center randomized trial, these investigators compared the therapy with carvedilol either before (n = 38) or after (n = 40) perindopril in newly diagnosed HF patients with idiopathic dilated cardiomyopathy. At 12 months, the group receiving carvedilol as initial therapy achieved a higher tolerable dose of carvedilol, a lower dose of furosemide, and better improvements in symptoms, left ventricular (LV) EF, and plasma N-terminal pro-brain natriuretic peptide (BNP) concentrations. These results argue that initiation of therapy with a beta-blocker prior to an ACEI may be preferable for HF.

Association between insulin resistance and cardiac dysfunction. Although insulin resistance has been shown to be a risk factor for ischemic cardiomyopathy, its role in the pathogenesis of idiopathic dilated cardiomyopathy (IDCM) has been uncertain. Witteles et al. (23) studied glucose metabolism in 43 consecutive patients with IDCM who were not diabetic and who did not have significant comorbid conditions. Compared to matched controls, plasma glucose responses were significantly higher during an oral glucose tolerance test in IDCM patients and this was associated with significantly higher plasma insulin concen-

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trations. These findings raise the possibility of a causal link between the two conditions. Although further verification of this association is needed, these findings could be of importance given the rising incidence of type II diabetes in the population.

Role of adrenergic genotype in modulating cardiac sympathetic drive and heart rate in HF. Overactivation of the sympathetic nervous system occurs in HF and plays an important pathophysiologic role in the progression of this condition. Functionally relevant polymorphisms of the alpha-2, beta-1, and beta-2 adrenoceptors have been identified. Kaye et al. (24) determined the beta-1, beta-2, and alpha-2C adrenoceptor genotype in 60 patients with severe congestive heart failure (CHF) in conjunction with measurement of cardiac and systemic sympathetic activity using the radiotracer norepinephrine spillover method. They demonstrated a strong relationship between heart rate and the level of cardiac adrenergic drive. Moreover, for a given level of cardiac adrenergic drive, heart rate was substantially greater in patients with the Arg/Arg16 beta-2 adrenoceptor polymorphism but not for polymorphisms of the beta-1 adrenoceptor. The genotype of the alpha-2C and beta-2 adrenoceptors, which are both located pre-junctionally, was not, however, related to the rate of norepinephrine release from cardiac sympathetic nerves. These findings provide the initial evidence that beta-2 adrenoceptor polymorphisms significantly influence the relationship between heart rate and cardiac adrenergic drive in HF patients. These findings have potential clinical relevance in that they may help explain the greater (or lesser) sensitivity of certain individuals to the development of HF and could indicate which patients are more likely to derive benefit from adrenergic-blocking agents.

An indication that genotyping of HF patients for certain polymorphisms might be important in helping to determine therapy was contained in a report from McNamara et al. (25) who evaluated the interaction of ACEI therapy with the effect of the ACE D/I polymorphism on HF survival. The ACE deletion allele (ACE-D) is associated with increased ACE activity and presumably higher levels of angiotensin II. In this prospective study, 479 subjects with systolic dysfunction were divided based on ACE inhibitor therapy into low dose (≤50% of target dose, n = 227), standard dose (>50%, n = 201), or those receiving angiotensin receptor antagonists (n = 51). The investigators found that the ACE-D allele was associated with an increased risk of events but that this effect was primarily in the low-dose group. Furthermore, the impact of beta-blockers and a high dose of ACEIs was greatest in subjects with the ACE DD genotype and was less apparent with the II and ID genotypes. Thus, evidence that higher doses of ACEIs diminished the impact of the ACE D allele, and that the benefits of beta-blockers and high-dose ACEIs appeared maximal for DD patients, suggests that determining ACE genotype may help target therapy for patients with HF in the future.

Selection of patients for cardiac transplantation in the current era of HF therapy. Recent advances in therapy have greatly improved the clinical course of HF patients. To determine how these changes might affect the selection of patients for cardiac transplantation Butler et al. (26) evaluated the relationship between survival, peak exercise Vo_2, and Heart Failure Survival Score (HFSS) in the current era of HF therapy compared with survival post-cardiac transplantation in 320 patients followed from 1994 to 1997 (past-era) and 187 patients followed from 1999 to 2001 (current-era). Outcomes were compared between these two groups and patients who underwent cardiac transplantation between 1993 and 2000. The investigators found that survival with medical therapy in the past era was 78% at one year and 67% at two years compared with 88% and 79%, respectively, in the current era (both $p < 0.01$) and that survival was improved in the current era regardless of peak Vo_2. Of interest was the finding that with current therapy 55% of patients with peak Vo_2 10 to 14 ml/min/kg had a low-risk HFSS and that this group exhibited an 88% one-year event-free survival which was similar to results reported with cardiac transplantation. These results suggest that improved survival for HF patients in the current era should lead to re-evaluation of the criteria used for listing for cardiac transplantation.

ECHOCARDIOGRAPHY

Although echocardiography is now well incorporated into daily practice, new approaches including three-dimensional echocardiography, contrast echocardiography, and tissue Doppler imaging are emerging as important clinical applications.

Stress echocardiography. Although stress echocardiography is well established in the assessment of CAD, several reports published in 2004 expanded the role for this technique in complex clinical settings. Bergeron et al. (27) studied the role of exercise echocardiogram (ExE) in predicting the outcome of patients referred for testing due to dyspnea. They compared the results of ExE in 443 patients with unexplained dyspnea to that of 2,033 patients with chest pain and 557 patients with both symptoms. Patients referred for dyspnea alone were older and had more cardiovascular abnormalities than the other groups. Ischemia on ExE was found in 42% of patients with dyspnea, 19% of patients with chest pain, and 58% with both symptoms. During 3.1 years of follow-up, cardiac death and nonfatal MI occurred more often in patients with dyspnea. Thus, this study demonstrated that patients referred for ExE for unexplained dyspnea have a high likelihood of myocardial ischemia and an increased incidence of cardiac events as compared to other patient cohorts, establishing an important role for ExE in this clinical setting.

In another study, Hillis et al. (28) examined the response of akinetic segments to exercise testing with echocardiography. Although the appearance of a new contractile abnor-

mality with exercise is clear evidence of myocardial ischemia, the response of akinetic segments was less well defined. Of 1,005 consecutive patients, 10% developed dyskinesis during exercise, and these more often manifested prior MI, a blunted blood pressure response, and electrocardiographic (ECG) ischemia than those in whom akinesis was unchanged. However, all-cause mortality and major cardiac events were similar over a median of 2.7 years. Thus, although patients in whom akinetic segments become dyskinetic manifest evidence of more severe ischemic heart disease, their overall prognosis is not adversely affected in the near term.

Reis et al. (29) evaluated the role of dobutamine stress echocardiography (DSE) in risk stratification of patients with rheumatic mitral stenosis. In 53 patients followed for a mean of 5 years, mean mitral valve gradient and peak dobutamine infusion was the best predictor of clinical events, and a mean gradient of 18 mm Hg at peak exhibited a sensitivity of 90% and specificity of 87% in predicting subsequent clinical events. Thus, DSE may have a role in identifying patients with mitral stenosis who are candidates for interventional therapy.

Three-dimensional echocardiography (3DE). Although the clinical applications of real-time 3DE imaging are not fully defined, the most immediate impact was predicted to be enhanced quantitation. Kuhl et al. (30) validated a combination of 3DE and a semi-automated border detection algorithm in quantitating LV volumes and function. The results of manual tracing and the border detection algorithm were compared to cardiac magnetic resonance imaging (CMR). Both approaches to 3DE data correlated well with CMR ($r = 0.98$), with a small standard error of the estimate. In another study, Jenkins et al. (31) examined the ability of 3DE to reduce the variability of LV size and function measurements obtained by ultrasound. Fifty patients underwent separate two-dimensional echocardiogram (2DE) and 3DE performed by different sonographers within 1 h, and results were compared to CMR. Measures of LV function and EF by both 2DE and 3DE correlated well with CMR, although echocardiography often manifested a systematic underestimation. Importantly, the variation in measurements exhibited by 2DE was substantially reduced by the three-dimensional technique. Thus, these studies demonstrated that real-time 3DE can reduce the inter-test variation in the assessment of LV size and function and, therefore, yield a more robust method for serial observation and assessing interventions.

Tissue velocity imaging. Although the ability to measure intrinsic myocardial velocity by Doppler tissue imaging (DTI) has been available for some time, new applications and the derivation of strain rate have increased the clinical role, especially the assessment of ventricular asynchrony. Thus, Bader et al. (32) evaluated DTI abnormalities as independent predictors of cardiac events in HF patients. In 104 patients with LV EF <45%, they measured interventricular and LV intraventricular regional electromechanical delays and catalogued the incidence of hospitalization for decompensation. They found that intra-LV but not interventricular asynchrony predicted cardiac events. Importantly, a weak correlation existed between QRS width and asynchrony by DTI, and 56% of patients with a QRS width of <120 ms manifested intra-LV asynchrony. Thus, the detection of intra-LV asynchrony by DTI measurements can identify HF patients at increased risk of decompensation.

A number of studies utilized DTI to identify HF patients who will benefit from cardiac resynchronization therapy (CRT). Bax et al. (33) reported on 85 end-stage HF patients with left bundle branch block (LBBB) and QRS >120 ms in whom clinical class, exertional capacity, and LV size and function were determined at 6 months and death and rehospitalization were ascertained at 1 year. The receiver-operating characteristic (ROC) curve analysis demonstrated that optimal separation of the 74% of responders from 26% of nonresponders occurred with a cutoff value of 65 ms of dyssynchrony manifested by a delay between the time to peak systolic velocity of the septum and lateral wall.

In another study, Bordachar et al. (34) evaluated the relationship between cardiac output and ventricular dyssynchrony parameters in patients undergoing CRT. They found that cardiac output correlated optimally with intraventricular delays in the time to onset of systolic velocity or time to peak systolic velocity. In patients in whom optimal pacing minimized dyssynchrony, reverse LV remodeling was observed at three months. Thus, these studies demonstrate that tissue velocity imaging can play an important role in identifying patients likely to respond to CRT, and in guiding the optimal pacing strategy to be applied. The mechanism by which CRT reduces mitral regurgitation (MR) was evaluated by Doppler velocity imaging by Kanzaki et al. (35). In 26 patients with at least mild MR who underwent CRT, regurgitant volume decreased from 38 to 22 ml. This reduction was significantly correlated with a shortening in the time delay between the insertion sites of the papillary muscles ($r = 0.77$). Thus, CRT produced an immediate reduction in MR that correlated with the timing of mechanical activation of the papillary muscle insertion sites, providing a feasible mechanism for this effect by CRT.

In another report, measurements of positive pre-ejection velocity derived from tissue velocity imaging were applied to predict a recovery of LV function after recanalization of an occluded coronary artery by Penicka et al. (36). They studied 43 patients with MIs due to an occluded coronary artery in whom revascularization was achieved. They observed that a positive pre-ejection velocity exhibited a sensitivity and specificity of 91% and 71%, respectively, in identifying dysfunctional segments that improved at three months. Thus, tissue velocity imaging provides criteria with which to predict the recovery of function in dyssynergic segments following revascularization.

Finally, Hillis et al. (37) assessed whether the ratio of early diastolic blood flow (E) to mitral annular (e′) by DTI,

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which has been shown to predict LV filling pressures can predict survival following AMI. The current study demonstrated that patients in whom the E/e′ was >15 manifested a 4.8 risk ratio for all cause mortality, thereby providing incremental prognostic information to other echocardiographic measurements.

Contrast echocardiography. Several studies reported last year provided evidence of the increasing usefulness of contrast echocardiography in clinical practice. Malm et al. (38) applied contrast echocardiography in an attempt to increase the accuracy and reproducibility of LV size and function measurements. They compared standard and contrast-enhanced 2DE against CMR in 110 consecutive patients. They found that limits of agreement between echocardiography and CMR narrowed significantly with contrast from 8.3% to 4.1% for LV EF. Importantly, the variability in the readings of two observers for LV EF was reduced considerably from standard echocardiography (14%) to contrast-enhanced echocardiography (7%), and intraobserver variability for LV EF decreased from 7.8% to 2.4%. Thus, this study demonstrated that the use of LV opacification by contrast echocardiography can yield measurements of LV size and function that are comparable in reproducibility to CMR. In another study, Kirkpatrick et al. (39) applied contrast echocardiography to differentiate cardiac masses due to thrombi from those due to tumors. They exploited the greater vascularity of tumors and demonstrated an increased signal intensity of tumors following contrast injection that was not visualized in thrombi.

Although most myocardial contrast echocardiography (MCE) protocols that identify CAD have utilized vasodilators, the standard agent for stress echocardiography is dobutamine. Elhendy et al. (40) injected boluses of ultrasonic contrast intravenously at immediate and peak stress during DSE in 170 patients undergoing coronary angiography. Overall, the diagnostic accuracy was higher for MCE than wall motion abnormalities on unenhanced echocardiography (81% vs. 71%; $p < 0.01$) and the sensitivity was greater for detecting abnormalities in multiple vascular regions. Thus, the bolus injection of ultrasonic contrast during DSE can provide enhanced diagnostic accuracy in assessing CAD. The need for enhanced quantitation of MCE was examined by Yano et al. (41). To address the heterogeneity of intensity among individual myocardial segments during MCE, these investigators derived measurements from both the subendocardium and adjacent LV cavity for individual segments. The calibrated intensity obtained by subtracting cavity from myocardial intensity of each segment reduced inter-segmental differences from 16 to 6 dB. As pointed out in an accompanying editorial by Lindner and Sklenar (42), the development of semi-automated quantification programs is driven by the need to enhance the performance of the human interpreter, and approaches such as those of Yano et al. (41) will be of value in this regard.

Transesophageal and intravascular echocardiography. The treatment of prosthetic valve thrombosis continues to present a clinical challenge. Tong et al. (43) reported the evaluation of transesophageal echocardiography (TEE) to provide risk assessment of thrombolysis of prosthetic valve thrombosis from the international Prosthetic Valve Thrombolysis Role of Transesophageal Echocardiography (PRO-TEE) registry. Of 107 patients from 14 international centers who presented with suspected prosthetic valve thrombosis and underwent TEE followed by thrombolysis, extension of thrombosis beyond the valve ring and the area of the thrombus proved to be predictors of complications. However, only thrombosis area was an independent risk stratifier. Thus, findings from TEE can be important in predicting complications from thrombolytic therapy of prosthetic valves. Hamilton et al. (44) presented data on the ability to image atheromas by combined administration of targeted echogenic immunoliposomes and intravascular ultrasound. In atherosclerosis produced in mini swines, these investigators were able to observe enhancement following the injection of anti-adhesion molecules, anti-tissue factor, and anti-fibrinogen conjugated echogenic immunoliposomes. These data point to a potentially important role for echocardiography in the molecular imaging of atherosclerotic plaques.

CAD RISK ASSESSMENT

Dekker et al. (56) studied the predictive value of heart rate corrected QT interval (QTc) for incident coronary heart disease (CHD) and cardiovascular disease (CVD) mortality in 14,548 black and white men and women age 45 to 64 years. Their results indicated that the age-, gender-, and race-adjusted hazard ratios for CVD mortality and CHD in subjects with the longest 10% relative to the other 90% of the gender-specific QTc distribution were 5.13 and 2.14, respectively. They noted that the increased risk was partly, but not completely, attributable to other risk factors or the presence of chronic disease. The association was stronger in black than in white subjects. In an accompanying editorial comment, Okin (57) noted that although additional study is required to clarify the meaning and mechanisms of a prolonged QTc, the Dekker et al. (56) findings strongly support the value of careful, quantitative electrocardiography in the application of QTc prolongation for risk stratification in the general population.

Sachdev et al. (58) considered the long-term prognostic importance of comorbid illness by examining a cohort of 1,471 patients with CAD who underwent cardiac catheterization between 1985 and 1989 and were followed through 2000 in the Duke Databank for Cardiovascular Diseases. A new CAD-specific index was created by assigning weights to individual diseases according to their prognostic significance using Cox proportional hazard models. The new index was compared with the widely used Charlson index, which is not specific to CAD, and was found to have a

remarkably similar prognostic significance in the Duke population. In an accompanying editorial comment, Hlatky (59) noted the new CAD-specific index has considerable face validity, and that "the CAD-specific index is likely to be a very useful measure in studies of mortality among patients with coronary disease."

Scuteri et al. (60) evaluated whether the clustering of multiple components of the metabolic syndrome has a greater impact on vascular thickness and stiffness than the individual components. They studied 471 participants from the Baltimore Longitudinal Study on Aging without clinical CVD. They concluded that the components of the metabolic syndrome interact to synergistically impact the vascular parameters. In an accompanying editorial comment, Domanski and Proschan (61) noted that the metabolic syndrome is a series of synergistically interacting risk factors for CVD, many or all of which may share a common etiology. They also suggested that delineation of the etiology of the syndrome, and its heterogeneity, will be useful in refining prevention and treatment strategies.

NUCLEAR CARDIOLOGY, CARDIAC CT, AND CMR

Single-photon emission computed tomography (SPECT). For purposes of diagnosis, Bayesian analysis dictates that myocardial perfusion SPECT (MPS) is best applied in patients with an intermediate likelihood of having CAD; for purposes of risk assessment in chronic CAD, the technique is commonly employed in patients with known CAD. Two studies published in *JACC* in 2004 supported the application of this method to patients with a high likelihood of CAD. Hachamovitch et al. (62) reported the prognostic and cost implications of stress MPS in 1,270 patients referred for exercise or adenosine MPS without known CAD but with a high pretest likelihood (>0.85) of CAD based on age, gender, symptoms, and CAD risk factors. Normal MPS was found in 47% of the patients studied, and in those treated without early revascularization, it was associated with low risk of cardiac death and hard events (0.6% and 1.3%/year, respectively). With increasing extent and severity of MPS defects, the risk of events increased significantly. Compared with strategies of initial referral to exercise testing, initial referral to MPS was a more cost-effective strategy in these patients. Of additional interest, this study documented for the first time that the current pattern of clinical use of MPS has created a referral bias to revascularization of most ischemic patients, which results in underestimation of the prognostic value of MPS when only non-revascularized patients are considered in studies.

Poornima et al. (63) reported similar findings in a related patient group but defined differently—by applying a rule-based clinical score to define patient risk. They studied the value of MPS in 1,461 symptomatic patients with a low Duke Treadmill Score (DTS) who were further stratified using a validated clinical score (CS) in which points were assigned for male gender, history of MI, diabetes, insulin use, and age (each decade over 40 years). In patients with low clinical risk (CS <5), the seven-year cardiac survival was 99%, even when the MPS was abnormal. A high risk CS (≥5), was found in 303 patients (21%). In these patients, a group analogous to those with a high likelihood of CAD in the study by Hachamovitch et al. (62), the annual cardiac mortality was not low (>1%), and MPS had independent prognostic value. The results of these two studies show that a stress MPS strategy is a reasonable alternative to direct referral to catheterization in patients with high clinical risk, defined either by the likelihood of CAD or a rule-based scoring approach.

Coronary calcium. Assessment of coronary artery calcium (CAC) using electron beam or multidetector spiral computed tomography (MSCT) has become commonly employed as a noninvasive method for assessment of coronary atherosclerosis, with impact on patient prognosis and management. The relationship between CAC and ischemia by noninvasive testing is less well understood. Berman et al. (64) assessed the 1,195 consecutive patients with no history of CAD who had CAC and stress MPS. Among patients with a calcium score <100, MPS ischemia was rare, occurring in <2% of such patients. As the CAC score increased, the frequency of myocardial ischemia on MPS increased progressively, becoming intermediate with CAC scores >400. The likelihood of myocardial ischemia by MPS was more tightly related to the absolute CAC score than age- and gender-stratified CAC percentile score. Importantly, in the 1,119 patients with normal MPS, a large proportion had high enough CAC scores that there would be consensus that aggressive medical management is warranted: 56% had CCS >100 and 31% had CCS >400.

Thus, low CAC scores appear to obviate the need for subsequent noninvasive testing. Patients with normal MPS, however, frequently have extensive atherosclerosis by CAC criteria, implying a potential role for applying CAC screening *after* a normal MPS study. Further assessment of atherosclerotic burden by CAC testing in patients with normal MPS may be useful in assessment of the need for aggressive medical therapy and dietary and exercise measures to prevent coronary events.

Multislice CT. Recent technical advances in MSCT scanners have begun to make the noninvasive CT coronary angiogram a clinical reality. Several clinical manuscripts in *JACC* in 2004 provided new evidence regarding the accuracy of CT coronary angiography with these recent generation CT scanners compared with catheter-based coronary angiography (65–68). Mollet et al. (65) prospectively evaluated the diagnostic performance of a recent generation MSCT scanner—a 16-slice CT scanner with rotation time of 420 ms—in 128 patients with chest pain in sinus rhythm scheduled for conventional coronary angiography, employing a 100 ml intravenous injection of iodinated contrast over 25 s. The diagnostic performance of MSCT coronary angiography was compared with quantitative coronary angiography (QCA). The sensitivity and specificity for detec-

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tion of individual coronary stenoses (≥50%) was 92% and 95%, respectively. On a patient basis, all patients with and 86% of patients without significant lesions on QCA were correctly classified by MSCT, as were all patients with significant left main stenosis or total occlusions.

Scanners have recently become available providing rotation times of <350 ms (implying half-rotation true tomographic imaging in about 175 ms) and broad coverage so that computed tomographic angiography can be completed in about 10 s or less. While previous generation scanners could only be used with high success rates in patients with heart rates <65 beats/min, the fast rotation times will allow somewhat higher heart rates. These new CT scanners provide true three-dimensional data with voxel dimensions as low as 0.4 mm. The broader spatial coverage of these scanners will result it scan times as short as 5 to 10 heart beats, and will require less intravenous contrast. Despite these highly encouraging results and developments, the approach will require relatively low heart rates, regular rhythm, and careful attention to quality control. Additionally, assessment of the coronary lumen in the presence of a coronary stent may still prove problematic, and even the highest resolution scanners available are unable to detect coronary stenosis areas with dense calcification.

Assessment of vascular reactivity. Although identification of the anatomic severity of coronary stenosis remains of great clinical importance, there has been burgeoning interest in the dynamic aspects of vascular lesions. Increasingly, endothelial dysfunction has been recognized as important in the pathophysiology of atherosclerosis. Flow-mediated vasodilation (FMD) of the brachial artery has received great attention in this regard; nonetheless, the assessment of FMD still remains more of research than of general clinical interest, due in large part to technical challenges presented by current ultrasound approaches or previous strain-gauge venous impedance plethysmography methods. Dupuis et al. (69) reported a highly original and simple imaging method that appears to be measuring FMD in conjunction with a routine that can be incorporated into a standard clinical myocardial perfusion protocol. The researchers evaluated the feasibility and validity of quantifying the hyperemic response in the forearm after injection of a technetium-99m tetrofosmin, a radiopharmaceutical in widespread use for MPS. A standard dose of tetrofosmin was injected following 5 min of right-arm ischemia. The forearms were then imaged using a standard nuclear medicine camera for 10 min, beginning 30 s after injection. The scintigraphic hyperemic reactivity was then assessed from the ratios of parameters from the activity-time curves between the forearms. In 46 patients with CAD compared to 47 patients without evidence of CAD, the hyperemia ration predicted the presence of CAD with a sensitivity of 70% and a specificity of 60%.

Differences on the order of 40% to 50% in the ratio of maximal upslope between the arms were the most predictive of the presence of CAD. The clinical importance of this interesting approach will await validation that the method correlates well with traditional methods of assessing FMD as well as further assessment as to whether this method provides significant incremental diagnostic, prognostic, or management information over that provided by the associated MPS examination.

Delayed enhancement. Cardiac magnetic resonance continues to offer great promise in clinical cardiology. The area in which this method has had the largest clinical impact is in imaging of MI or scarring by gadolinium delayed enhancement (DE). A large body of literature in animal and human studies has documented that this approach is highly sensitive and specific for infarcted or scarred myocardium. Several studies in *JACC* in 2004 have broadened our understanding of the phenomenon of DE (70–73). Moon et al. (70) used the assessment of DE to determine the pathological basis of Q-wave myocardial infarction (QWMI) and non–Q-wave myocardial infarction (NQWMI). The investigators studied 100 consecutive patients with pervious MI who had ECG and CMR on the same day; patients with acute MI within seven days were excluded. Size and transmural extent of MI were quantified by DE CMR. Subendocardial and transmural components were common in both QWMI and NQWMI; fully 99% of patients with QWMI had at least some of their infarct in a subendocardial distribution and 28% of patients with a NQWMI had regions of infarct that were transmural. As the size and number of segments with transmural MI by DE increased, the probability of Q waves increased; however, the total size of MI by DE was the strongest predictor of Q waves, and when it was considered, the transmural extent of MI was not an independent predictor. Although the division into QWMI and NQWMI is useful because the former predicts a larger MI, the findings of this study (70) show that the division into transmural and non-transmural MI is less meaningful.

CAD

Markers. The search for more sensitive and earlier markers in the diagnosis of AMI continued in 2004. Recognizing the role of inflammation in unstable angina and MI, Patti et al. (74) evaluated serum levels of the inflammatory mediator interleukin-1 receptor antagonist (IL-1RA) in 44 patients with MI. They found that IL-1RA levels were elevated earlier in the course of MI than the commonly available biomarkers such as myoglobin and troponin. The sensitivity in patients presenting <3 h from onset of symptoms was 86% and was 91% in patients with heralded infarction.

B-type natriuretic peptide continued to be a focus of continued intense investigation. Logeart et al. (75) studied 107 HF patients. The predischarge BNP assay had better discriminative power (area under the ROC curve = 0.80) than EF and other clinical parameters. The risk of death or re-admission increased in stepwise fashion with increasing predischarge BNP levels ($p < 0.0001$).

In follow-up to an earlier report, Landesberg et al. (76) provide additional data regarding markers and non-cardiac surgery. They demonstrated that troponin elevations are common after such surgery, strongly associated with post-operative ischemia, predicted by inducible ischemia on preoperative thallium scanning, and, most importantly, are reduced by preoperative coronary revascularization.

Inflammation. Inflammation continued to attract attention as a central pathophysiologic mechanism not only in coronary disease but also in other CVDs such as aortic valve disease. Chandra et al. (77) compared inflammatory markers and CAD in patients with and without aortic sclerosis in a cohort of 415 patients being evaluated for acute chest pain. Aortic sclerosis was present in 49% of these 415 patients, a higher prevalence than seen in population-based studies, most likely due to the selection of patients with cardiac symptoms. There was an increased rate of cardiovascular events, defined as cardiovascular death or CAD, at one year in those with aortic sclerosis (16.8% vs. 7.1%, $p = 0.002$). However, in multivariate analysis aortic sclerosis was no longer a significant risk factor, whereas CAD, advanced age, HF, and C-reactive protein (CRP) levels remained significant. The investigators concluded that the increased incidence of adverse cardiovascular events in patients with aortic sclerosis is associated with CAD and inflammation, not a result of the effects of valvular heart disease per se.

Inflammation also appears to play an important role in advanced aortic stenosis. In an immunohistological study on valves excised at surgery, Mazzone et al. (78), found that advanced "degenerative" aortic valve stenosis appears to be a chronic inflammatory process associated with atherosclerotic risk factors. The researchers detected the coexistence of neoangiogenesis, T-lymphocyte infiltration, adhesion molecules, and *hsp60* gene expression. These inflammatory findings were absent in a control group of valves excised owing to diseases of the proximal aorta.

Although most studies have focused on inflammatory mediators and markers, there is also increased awareness that as in most biological systems there are both pro-inflammatory and anti-inflammatory processes in play. A particularly interesting anti-inflammatory mediator is IL-10. Fichtlscherer et al. (79) studied endothelial function in 65 male patients with CAD. They not only found that IL-10 levels correlated positively with endothelial function, but also that even in the presence of elevated CRP levels endothelial function was preserved. This "ying-yang" (80) points to a balance of inflammation and anti-inflammation in the body.

Anti-inflammatory effects may also be mediated by dietary intervention. The Mediterranean diet has been shown to reduce cardiovascular risk, but the mechanisms underlying this effect has not been fully elucidated. In a study from Greece (81) with over 3,000 participants, those in the highest tertile of adherence to a Mediterranean diet had, on average, 20% lower CRP levels ($p = 0.015$), 17% lower IL-6 levels ($p = 0.025$), 15% lower homocysteine levels ($p = 0.031$), 14% lower white blood cell counts ($p = 0.001$), and 6% lower fibrinogen levels ($p = 0.025$), as compared with those in the lowest tertile.

Platelet/aspirin resistance. The role of platelets in inflammation has emerged as an important aspect of atherothrombosis. One of the platelet-derived mediators of inflammation is the CD40-ligand (CD40L), with platelets being the main source of its soluble form. Understanding the mechanisms underlying soluble CD40L release from platelets was aided through a study by Furman et al. (82). They demonstrated that, whereas translocation of CD40L to the cell membrane is not dependent on GP IIb/IIIa, its release is mediated through GP IIb/IIIa and inhibited by the GP IIb/IIIa receptor antagonists abciximab, eptifibatide, and tirofiban.

Resistance to antiplatelet agents (both aspirin and clopidogrel) emerged as an important area of investigation. Pulcinelli et al. (83) prospectively studied 150 patients on aspirin as well as 80 patients prescribed ticlopidine. Platelet function was periodically monitored before and after 2, 6, 12, and 24 months. Aspirin demonstrated an antiplatelet effect at two months, Thereafter, however, this inhibitory effect progressively decreased. At 24-month follow-up, collagen-induced platelet aggregation was significantly higher than that observed at 2 months ($p < 0.05$). Conversely, the inhibition induced by ticlopidine was constant throughout follow-up. Thus, long-term aspirin therapy was shown to be associated with tachyphylaxis.

Does clopidogrel treatment eliminate the problem of aspirin resistance? At least in patients undergoing elective PCI the answer appears to be no. Chen et al. (84) used the Ultegra Rapid Platelet Function Assay-ASA to determine aspirin responsiveness of 151 patients scheduled for non-urgent PCI. All patients received a 300-mg loading dose of clopidogrel >12 h before and a 75-mg maintenance dose in the morning of the PCI. Twenty-nine (19.2%) patients were found to be aspirin-resistant, with a significantly higher incidence of females in the aspirin-resistant versus aspirin-sensitive groups. The incidence of any creatine kinase-myocardial band (CK-MB) elevation was 51.7% in aspirin-resistant patients and 24.6% in aspirin-sensitive patients ($p = 0.006$). Thus, despite pretreatment with clopidogrel, patients with aspirin resistance as measured by a point-of-care assay demonstrated an increased risk of myonecrosis following non-urgent PCI.

The search for a better aspirin was highlighted in a study on the innovative compound NCX-4016 by Fiorucci et al. (85) in 46 volunteers. The NCX-4016 is an aspirin derivative containing a nitric oxide-releasing moiety that blocks platelet activation and modulates tissue factor (TF) expression and cytokine release from lipopolysaccharide (LPS)-stimulated monocytes. The investigators demonstrate less gastric damage, equal platelet inhibition, while preventing monocyte activation.

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Metabolic syndrome/obesity and overweight/dyslipidemia. Given the pandemic and cardiac implications of obesity and being overweight, it is not surprising that many studies addressed this vital issue.

The importance of the metabolic syndrome in cardiac disease was underscored by an analysis of a prospective study of 1,742 hypertensive subjects by Schillaci et al. (86). Event rates in the groups with one to five characteristics of the metabolic syndrome were 1.54, 1.96, 2.97, 3.35, and 5.27 per 100 patient-years, respectively ($p < 0.001$). A total of 593 patients (34%) had the metabolic syndrome. Patients with the syndrome had an almost double cardiovascular event rate than did those without (3.23 vs. 1.76 per 100 patient-years, $p < 0.001$).

On a basic level it has been recognized that adipose tissue, once thought to be an inert organ that simply stored fat, is an important regulator of metabolism and inflammation, through the secretion of various cytokines, including leptin and adiponectin. The latter is believed to have anti-diabetic and anti-atherosclerotic effects. In a report by Ohashi et al. (87), the genetics of adiponectin and its effects on coronary disease were explored. The investigators demonstrated that the I164T polymorphism for the adiponectin gene was associated with low adiponectin levels, the metabolic syndrome, and CAD. As for leptin, Wolk et al. (88) demonstrated in a study of 361 patients with angiographic coronary disease that leptin levels predicted future cardiovascular events, independent of lipid levels and CRP.

Although low-density lipoprotein (LDL) cholesterol is recognized as a key risk factor for atherosclerosis, the role of other lipid particles has also received rightful attention. Two studies addressed the role of remnant lipoproteins (RLP) in atherosclerosis. Fukushima et al. (89) demonstrated that patients with CAD had higher RLP levels than patients without CAD. Moreover, Kaplan-Meier analysis demonstrated that higher RLP cholesterol levels in patients with CAD resulted in a significantly higher probability for the development of coronary events. An accompanying study by Sposito et al. (90) addressed some of the underlying mechanisms in remnant metabolism. They followed 63 CAD patients in whom kinetic studies of the in vivo catabolism of chylomicron-like emulsions were performed with comparison to a control population. At enrollment into the study, fasting patients were injected intravenously with a chylomicron-like emulsion labeled with radioactive triglyceride (^{3}H-TG) and cholesteryl esters (^{14}C-CE) to evaluate the efficacy of intravascular triglyceride (TG) lipolysis. The CAD patients demonstrated impaired intravascular TG lipolysis and this impairment correlated with adverse clinical events in the CAD group.

Aging. Why do elderly patients with MI have a worse prognosis? The role of collaterals was assessed by Kurotobi et al. (91) in 1,934 patients undergoing coronary angiography within 72 h of their AMI using the Rentrop score. The investigators found that the prevalence of collaterals decreased with age. Multivariate analysis showed that the absence of collaterals was an independent predictor of in-hospital mortality in elderly patients ≥70 years, although this finding was not significant in patients <70 years.

Clinical trials and therapeutics. With the ageing of the population the issue of stroke and attempts at reducing its devastating effects have gained urgency. Papdemetriou et al. (92), in a predefined subgroup analysis of 1,518 elderly patients (age 70 to 89 years) with isolated systolic hypertension in the Study on Cognition and Prognosis in the Elderly (SCOPE) trial demonstrated an impressive 42% reduction in stroke with the angiotensin receptor blocker candesartan in comparison with other antihypertensive treatment, despite little difference in blood pressure reduction. This finding confirms the benefit seen in a broader population in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.

The role of sildenafil, a phosphodiesterase inhibitor, in treatment of primary pulmonary hypertension was studied in a cross-over blinded study in 22 patients. Exercise time increased by 44% from 475 ± 168 s at the end of placebo phase to 686 ± 224 s at the end of the sildenafil phase ($p < 0.0001$). With sildenafil, cardiac index improved from 2.80 ± 0.9 l/m^2 to 3.45 ± 1.1 l/m^2 ($p < 0.0001$), whereas pulmonary artery systolic pressure decreased insignificantly from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mm Hg.

Despite their acceptance in guidelines as an important therapy in ST-segment elevation MI, the use of beta-blockers in primary PCI has not been studied in a randomized clinical trial, with clinical use based on extrapolation from pre-lytic and lytic trials. Three studies addressed this important issue in a retrospective manner. Mehta et al. (93) presented data from 3,065 patients in the PAMI trials. Lack of preprocedural beta-blocker use was found to be a risk factor for ventricular tachycardia (VT)/ ventricular fibrillation (VF) during primary PCI (odds ratio [OR] 2.34, 95% confidence interval [CI] 1.35 to 4.07). Similarly, data was presented by Nikolsky et al. (94) from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. A total of 1,136 patients (54.5%, BB+ group) received beta-blockers before PCI, whereas 946 (45.5%, BB− group) did not. The 30-day mortality was significantly lower in the BB+ group than in the BB− group (1.5% vs. 2.8%, $p = 0.03$), an effect entirely limited to patients who had not been receiving beta-blockers before admission (1.2% vs. 2.9%, $p = 0.007$). In contrast, no survival benefit with pre-procedural beta-blockers was detected in patients receiving beta-blockers at home (3.3% vs. 1.9%, respectively, $p = 0.47$). The use of post procedure beta-blockers was assessed by Kernis et al. (95) in 2,442 patients in the PAMI trials. They found that at six months, patients receiving beta-blockers were less likely to die (2.2% vs. 6.6%, $p < 0.0001$) or experience MACE (14% vs. 17%, $p = 0.036$). In multivariate analysis, beta-blockers were independently associated with lower six-month mortality.

ELECTROPHYSIOLOGY

Ablation of atrial fibrillation (AF). Recent studies have shown that areas of complex fractionated atrial electrograms (CFAEs) correlate with areas of slowed conduction and pivot points of reentrant wavelets that may perpetuate AF. Nademanee et al. (96) hypothesized that such areas of CFAEs could be identified and ablated, thus curing AF. The researchers, therefore, studied 121 patients, mean age 63 years, with refractory AF, 57 of whom had paroxysmal and 64 of whom had chronic AF. The investigators performed nonfluoroscopic electroanatomic mapping of both atria. CFAEs identified in these defined regions during AF were then ablated using radiofrequency (RF) energy until AF terminated or all areas with CFAEs were ablated. CFAEs were found in seven out of nine regions of both atria. Ablations of areas associated with CFAEs resulted in termination of AF without external cardioversion in 115 of 121 patients, although 32 required adjunctive therapy with ibutilide. A one-year total of 110 patients were free of AF and arrhythmia-related symptoms. The investigators concluded that atrial areas with CFAEs represent a defined electrophysiologic substrate and are ideal target sites for ablation to eliminate AF.

Chen et al. (97) determined the safety and efficacy of pulmonary vein isolation (PVI) using RF catheter ablation to treat AF in patients with impaired LV systolic function. Previously published data on PVI for treatment of AF has been limited to patients with normal LV function. The investigators retrospectively evaluated 94 patients with LV EF <40%, among 377 consecutive patients undergoing PVI between December 2000 and January 2003 at their institution. End points included AF recurrence, changes in LV EF and quality of life scores (QoL). After initial PVI, 73% of patients with reduced LV EF compared to 87% of patients with normal LV EF were free of AF recurrence at 14 ± 6 months ($p = 0.03$). In the study group, there was a small but statistically insignificant increase in EF of 4.6%, but a significant improvement in QoL. Complication rates were low and were not different between groups. Although the recurrence rate of AF after initial PVI in patients with reduced LV EF was higher than with normal LVEF, nearly three-fourths of patients with reduced LV EF remained free of AF during follow-up. The investigators suggest that PVI may be feasible in AF patients with reduced LV EF.

It is uncertain whether men and women differ in frequency of arrhythmia recurrence, and whether any observed gender differences are independent of clinical, ECG, and electrophysiologic (EP) characteristics (98). Lampert et al. (98) analyzed the clinical records and implantable cardioverter-defibrillators (ICDs) data disks of 340 men and 59 women with CAD who received an ICD capable of storing multiple arrhythmia episodes in memory. During an average follow-up of 30 ± 22 months, the investigators observed that sustained VT/VF occurred in 52% of men and 34% of women ($p < 0.01$), and that men experienced more total VT/VF events ($p < 0.01$), more shock-treated VT/VF events ($p < 0.03$), more episodes of electrical storm ($p < 0.001$), and had VT/VF on more days in follow-up ($p < 0.01$) compared to women. The observed gender differences were independent of all other clinical, ECG, and EP variables analyzed. Gender differences in VT/VF recurrence were greatest in patients with sustained monomorphic VT, and those with inducible VT at EP study. The researchers concluded that among the CAD patients with ICDs, women were significantly less likely to experience VT/VF, and had fewer VT/VF episodes, than men.

Cause of death in Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. Greenberg et al. (99) sought to identify the cause of sudden and presumably arrhythmic death versus non-sudden cardiac death, in the MADIT-II. To better understand the modes of death might lead to more rational and effective therapeutic interventions in such high-risk populations. The MADIT-II trial involved a 31% mortality decrease in 1,232 post MI patients and low EF (<30%) randomized to ICD implantation versus conventional medical therapy. A total of 202 deaths were evaluated, using a variation of the Hinkle-Thaler classification system as well as a clinical classification system. The sudden cardiac death rates were 10.0% in the conventional group and 3.8% in the ICD group ($p < 0.01$), with a hazard ratio for sudden cardiac death risk in the defibrillator group of 0.33 (95% CI 0.20 to 0.53; $p < 0.0001$). Sudden cardiac death made up 51% and 61% of the total and cardiac deaths, respectively, in the conventional therapy group compared with 27% and 35% in the ICD group. However, the ICD had no significant effect on non-sudden death. Thus, the data indicate that the decrease in mortality with ICD therapy in the MADIT-II is entirely due to a reduction in sudden cardiac death. However, lethal arrhythmias were confirmed as the cause of sudden cardiac death in the majority of cases. In future ICD trials the clinical classification of cardiac death should be integrated with the terminal rhythm from postmortem ICD interrogation to help identify patients who will not benefit from ICD therapy.

ICDs. Although the correct approach to management of asymptomatic patients with Brugada syndrome and inducible ventricular arrhythmias remains controversial, class Ia antiarrhythmic drugs, which inhibit the transient outward current (Ito) of the action potential, have been proposed as effective treatment. From a cohort of 106 patients with Brugada syndrome, Hermida et al. (100) studied 35 patients who received hydroquinidine. Patients had either asymptomatic Brugada syndrome with inducible arrhythmia (n=31) or were symptomatic with multiple ICD shocks. A "slow release" hydroquinidine was given 300 mg twice a day and was increased to 900 mg /day if patients were still inducible and had a plasma level <3 μmol/l. Hydroquinidine was observed to prevent VT/VF inducibility in 76% of asymptomatic patients who underwent EP-guided therapy. During 17 ± 13 months of follow-up, syncope occurred in

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2 of the 21 patients on hydroquinidine therapy. In asymptomatic ICD patients (n = 10), one patient received an appropriate shock during 13 ± 8 months of follow-up. In symptomatic patients with multiple ICD shocks, hydroquinidine prevented VT/VF recurrence in all cases during a mean follow-up of 14 ± 8 months. Thus, hydroquinidine therapy prevented VT/VF inducibility in the majority of asymptomatic patients with Brugada syndrome and VT/VF recurrence in all patients with multiple ICD shocks. The investigators suggest that treatment with hydroquinidine may be an alternative to ICD as primary preventative therapy in asymptomatic patients with Brugada syndrome and inducible arrhythmia. However, as the researchers note in their report, this study was not randomized or controlled, the number of patients was small and the follow-up duration short, and there was no ECG documentation of the cause of the clinical events in patients taking hydroquinidine.

It is uncertain whether AF is abolished by eliminating the initiating triggers by electrically isolating the pulmonary veins, or by preventing perpetuation of AF by altering left atrial EP substrate. It is also not known whether circular plus linear left atrial ablation produces an "all or none" response or modifies the number and duration of AF episodes. Kottkamp et al. (101) analyzed the duration of AF episodes before and after circular plus linear left atrial ablation, and the percentage of patients with complete freedom from AF after ablation, by comparing 24-h with 7-day ambulatory ECG monitoring. In 100 patients with paroxysmal (n = 80) or persistent (n = 20) AF, the relative period spent in AF decreased significantly over time from an average of 35% before ablation, to 26% immediately after ablation, to 10% after 12 months. Freedom from AF gradually increased in patients with paroxysmal AF after 12 months to 88% or 74% by 24-h or 7-day ECG monitoring. The investigators demonstrated complete pulmonary vein isolation (PVR) in <20% of subjects. The researchers concluded that circular plus linear left atrial ablation for the treatment of AF produced substrate modification as the main salutary mechanism and that this approach results in a delayed as opposed to immediate cure. The data also suggest that the use of longer duration monitoring produces a more accurate assessment of cure rates of ablation for AF.

To examine whether ICD utilization in survivors of cardiac arrest (CA) is adequate, Saba et al. (102) analyzed the incidence of ICD therapy in survivors of CA in the U.S. from 1996 through 2001. The National Hospital Discharge Survey (NHDS) was used to obtain data. The investigators searched for patients admitted with the primary diagnosis of CA who survived to hospital discharge. Patients with a concomitant diagnosis of AMI or prior ICD in situ were excluded. Of 49,517 patients who survived CA, 30.7% received an ICD before discharge, with a gradual increase in implantation rates from 1996 (23.6%) to 2001 (46.3%). Using logistic regression for the years 2000 and 2001, Saba et al. (102) determined that patients who were discharged without an ICD were older, more likely to be of African-American race, and more likely to be admitted to a smaller hospital. These predictors were independent of other comorbid illnesses. The authors concluded that, although gradually increasing during the period of study, rates of ICD implantations after CA still remain low, and that there are differences in implantation rates by race.

CONGENITAL HEART DISEASE

Ductus arteriosus. A controlled stenting of the ductus-arteriosus will provide a systemic to pulmonary shunt for babies with right-sided outflow obstruction and could provide a guaranteed systemic circulation for babies with left heart atresia or hypoplasia. The ductus is a dynamic structure, and opening it with a stent has caused complications such as constriction and/or ductal laceration. In a multicenter study, investigators from Leuven and Toronto reported a combined experience using 4-F, outer diameter coronary stents, 13 to 24 mm positioned within the duct (103). In 10 patients with ductal dependent pulmonary artery circulation, 13 stents were implanted with a mean fluoroscopy time of 9 to 58 min. There was adequate growth of the pulmonary arteries and gradual lumen narrowing of the ductus lumen through intimal hypoplasia. All of the patients later went on to the next stage of surgery. These long flexible stents appeared quite effective, but like coronary stents they were subject to neo-intimal proliferation. Postoperative patients with tetralogy of Fallot are at risk of functional deterioration in the face of significant added RV work if they have significant pulmonary insufficiency.

Pulmonary artery stents. Younes Boudjemline, in conjunction with Phillip Bonhoeffer, a pioneer of percutaneous valve development, report a self-expandable valve stent that can be deployed in a dilated RV outflow tract (104). The 30-mm diameter stent contains a bovine jugular vein valve mounted in an hour-glass constriction that provides a pulmonary valve annulus. One-step procedures put the valve directly in place while two-step procedures placed an outer stent and then the inner stent containing the valve. Eight of the ten devices were successfully delivered in ewes. Stepwise reduction in the pulmonary artery size was achieved as was valve implantation. Of the stents placed, there were no early or late migrations and no significant gradient. One group was studied immediately after implant and the other group was studied two months' post-implantation.

A study from the University of Chicago and Columbia University in New York by Pass et al. (105) reviews a 25-center experience of 484 patients from September 1999 to June 2002 who underwent ductal occlusion with the Amplatzer device. Of the 484 patients with ductus enrolled, no implantation was attempted in 45 patients. Implantation was successful in 435 of the 439 patients attempted, 329 of which resulted in complete closure. The patients' ages ranged from a little over 2 months to 70 years. Follow up of the 49 patients with residual shunts at 24 h showed 41 of 43

closed on echocardiography and remained closed for 6 months. This large study demonstrated that the widely used Amplatzer device, can effectively close moderate to large ductal shunts with excellent one year results.

Bicuspid aortic valve. A study from Ospedale Pediatrico Bambino Gesu and Boston Children's Hospital (106) reports an 11-year follow up of 1,135 pediatric patients <18 years of age diagnosed with bicuspid aortic valve from 1986 and 1999. The study relates aortic valve morphology and long-term status determined between 5 and 19 years after diagnosis. The vast majority of patients had right and left coronary leaflet fusion resulting in a horizontal aortic valve raphe, and this was also the most common form in those who had coarctation. Fusion of the right coronary and non-coronary leaflets with a vertical appearing commissure was associated with greater odds for both more significant gradient and/or more significant aortic regurgitation on echocardiogram at follow up. The study demonstrates that the risk factors for progression of isolated aortic valve disease are not the same for all bicuspid aortic valves.

Aortic complications of coarctation. Oliver et al. (107) studied 235 patients treated for coarctation treated either surgery or balloon angioplasty. Surgery was performed in 181 patients, balloon angioplasty without stenting in 28 and 26 patients were untreated. The investigators looked at other complications related to the aorta. There were 44 aortic wall complications resulting in death or the need for surgical intervention including ascending or descending aortic aneurysms, aortic rupture, false aneurysms, aortic dissection, or fistula. They examined quality of repair and type of repair as well as morphology of the aorta in their study. The complications of ascending or descending aneurysms were not specifically associated with the time or type of coarctation treatment. Thirty-seven of the patients had these serious complications; about 16% had false aneurysm, rupture, and dissection. The risk complications increased with age and was independently related to the diagnosis of bicuspid aortic valve. The study emphasizes that coarctation patients, even with good results, need ongoing surveillance because they have abnormal aortic structure. The abnormal aorta is stiff in these patients and pulse wave propagation is increased. The abnormal aortic structure makes them at risk for these types of complications. Recently, follow-up guidelines for coarctation in adults have emphasized the abnormal architecture of the aortic wall in coarctation and the needs for ongoing evaluation of patients.

Atrial septal defect (ASD) closure devices. A study by Krumsdorf et al. (108) from Frankfurt, reports the incidence and clinical course of thrombus formation on ASD or patent foramen ovale (PFO) closure devices in 1,000 consecutive patients who had PFO, 593 of who were ASD. Patients underwent closure with a variety of devices. All the patients had TEE after four weeks and six months with additional TEEs as clinically indicated. Patients received routine aspirin and clopidogrel. The incidence of thrombus formation was 7.1% on the Cardioseal, 5.7% on the Starflex device, 6.6% on the PFO star, and 0% on the Amplatzer device. Twenty-eight patients had thrombus formation on their device; in 17 of 20, the thrombus resolved under anticoagulation; in three patients the thrombus was removed surgically. Thrombus was most common on the left side of the device and occurred in 1.2% of ASD patients and 2.5% in PFO patients. Post-procedural AF and persistent atrial-septal aneurysm were significant predictors of thrombus formation. One patient had the Starflex device removed together with thrombus after suffering a stroke. Post-procedural shunt occurred in 15% of the patients with thrombus (3 of the 20), as did wire fracture on the right side of the septum.

PRECLINICAL STUDIES

Use of granulocyte macrophage-collagen stimulating factor (GM-CSF). Inflammatory responses after AMI affect LV remodeling. Maekawa et al. (45) examined the role of macrophages and monocytes by treating rats with romurtide, an inducer of GM-CSF, for one week after MI. Treatment increased circulating monocytosis and macrophage infiltration into the infarct, with adverse effects on remodeling, infarct expansion, decreased LV function, and increased mortality. These results have implications for the recent use of granulocyte and GM-CSF to mobilize endothelial progenitor cells, as discussed in an editorial comment (46). Stem cells may be harvested for injection into the infarct region to decrease infarct size, remodeling, and mortality. However, the simultaneous mobilization of monocytes and macrophages early after AMI may have the undesirable effects of exacerbating remodeling and mortality.

Apoptosis. Apoptosis is associated with MI and HF. However, it is unknown whether inhibiting apoptosis affects ventricular remodeling and/or alters the development of HF. Chandrashekhar et al. (47) examined these issues by inhibiting caspase, a key step in the apoptosis pathway, for four weeks following MI in rats. The inhibitor decreased caspase-3 activity, decreased cardiac apoptosis, and attenuated the decline in LV function and remodeling. Regulating apoptosis may be a novel therapeutic target to attenuate ventricular remodeling and improve ventricular function after an MI.

Postconditioning. Timely reperfusion is crucial for salvaging myocardium in AMI. The method of reperfusion also may affect the outcome. Yang et al. (48) used a rabbit infarct model to demonstrate that four 30-s cycles of reperfusion interrupted by reocclusion significantly decreased infarct size from 35% to 20% of the risk zone. This confirms the existence of a recently described phenomenon termed ischemic *postconditioning*, which has been demonstrated in different species. This has practical implications as the cardioprotective effects are elicited after ischemia has been established, whereas in the better-known ischemic *preconditioning*, beneficial effects are linked to events that occur

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prior to ischemia. As noted by Heusch in his editorial comment (49), postconditioning may involve both similar (e.g., K_{ATP}-channel) and different signaling pathways as ischemic preconditioning. Staged, controlled reperfusion strategies may provide additional benefits to improve outcomes with reperfusion.

Hibernation. Contractile and metabolic function in hibernating myocardium improves with the restoration of myocardial blood flow. Elsasser et al. (50) examined whether cell death occurs in chronic hibernating myocardium. Hibernating myocardium was documented in patients undergoing revascularization. Systematic analyses of tissue demonstrated increased cell death from apoptosis and autophagic cell death involving ubiquitin. The presence of multiple mechanisms for myocyte degeneration and cell death in chronic hibernating myocardium indicates that delays in restoring myocardial blood flow may allow irreversible cell death to limit the extent of functional recovery.

Myocardial regeneration. Stem cells and progenitor cells from different sources have been used to repair damaged myocardium after infarction, but there are scant data evaluating outcomes based on face to face comparisons. Agbulut et al. (51) found that transplantation of human skeletal myoblasts and bone marrow derived $CD133^+$ progenitor cells had comparable effects in improving LV function and inducing angiogenesis after infarction in mice. The equivalency in results despite differences in engraftment suggests differences in mechanisms. These results have important implications, as discussed by Dimmeler and Zeiher in their editorial comment (52). Cell types differ in their capacity to differentiate, engraft, secrete mediators, modify healing processes, and induce complications (e.g., arrhythmias). As alternative sources and clinical applications of stem and progenitor cells are sought, it will be a challenge to identify the best cells for cardiac regeneration and vascularization until the mechanisms for benefits are better understood and crucial safety issues are addressed.

Myocarditis. A study by Nishii et al. (53) demonstrated that serum interleukin (IL)-10 levels at the time of admission in patients with documented fulminant myocarditis are predictive of which patients are likely to need LV assist device implantation or go on to die from their disease. This is especially important in patients with fulminant myocarditis as there is a good chance of a favorable clinical outcome if the patients are supported through the severe hemodynamic compromise that accompanies their presentation. Furthermore, it demonstrates the potential value of serum biomarkers in myocarditis because similar findings did not occur in patients requiring hemodynamic support during MI. Although this study was performed on a relatively small number of patients, it was interesting that there was a cutoff value above which serum IL-10 levels predicted the likelihood of need for implantation of mechanical assist devices. The implications of this study were commented on in an accompanying editorial (54).

It has been previously demonstrated in genetic and viral forms of cardiomyopathy that alterations in the dystrophin glycoprotein complex can contribute to the pathogenesis of dilated cardiomyopathy. In a report by Vatta et al. (55), it was shown that disruption of the amino terminus of dystrophin can occur in patients with cardiomyopathy of ischemic or unknown etiologies. In addition, the investigators demonstrated that dystrophin localization to the sarcolemma is improved in both the LV and RV following ventricular assist device implantation. The improvement occurred with either pulsatile or continuous-flow ventricular assist devices. These findings suggest the possibility that disruption of the dystrophin glycoprotein complex may play a role in a broad spectrum of cardiomyopathies and demonstrate that improvement in this molecular phenotype in both ventricles occurs with implantation of a ventricular assist device.

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